

What is claimed is:

1. A soluble mutant flt3 ligand (flt3-L) polypeptide, wherein said polypeptide exhibits increased or decreased biological activity relative to the full length human wild type flt3-L polypeptide (SEQ ID NO:1) or mature flt3-L polypeptide (SEQ ID NO:18).

2. The polypeptide of claim 1, wherein said polypeptide comprises one or more amino substitutions in any one of the regions defined by the amino acid positions 8-15, 81-87, or 116-124 of the mature human wild type flt3-L polypeptide (SEQ ID NO:18).

3. The polypeptide of claim 1, wherein said polypeptide comprises one or more substitutions at position 8, 84, 118 or 122 of the mature wild type flt3-L polypeptide (SEQ ID NO:18).

4. The polypeptide of claim 1, wherein said polypeptide comprises one or more substitutions selected from the group consisting of L-3H (SEQ ID NO:10), H8Y (SEQ ID NO:11), W118R (SEQ ID NO:16), K84E (SEQ ID NO:14), K84T (SEQ ID NO:15) and Q122R (SEQ ID NO:17).

5. The polypeptide of claim 4, wherein said polypeptide comprises the L-3H (SEQ ID NO:10), H8Y (SEQ ID NO:11), K84E (SEQ ID NO:14) and Q122R (SEQ ID NO:17) substitutions.

6. The polypeptide of claim 1, wherein said polypeptide is a fusion protein with a second polypeptide, wherein said second polypeptide is selected from the group consisting of erythropoietin (EPO), thrombopoietin (TPO), granulocyte-macrophage Colony Stimulating Factor (GM-CSF), granulocyte Colony Stimulating Factor (G-CSF), an interleukin, immunoglobulin, and fragments thereof.

7. The polypeptide of claim 2, wherein said polypeptide is a fusion protein with a second polypeptide, wherein said second polypeptide is selected from the group consisting of erythropoietin (EPO), thrombopoietin (TPO), granulocyte-macrophage Colony Stimulating Factor (GM-CSF), granulocyte Colony Stimulating Factor (G-CSF), an interleukin, immunoglobulin, and fragments thereof.

8. The polypeptide of claim 3, wherein said polypeptide is a fusion protein with a second polypeptide, wherein said second polypeptide is selected from the group consisting of erythropoietin (EPO), thrombopoietin (TPO), granulocyte-macrophage Colony Stimulating Factor (GM-CSF), granulocyte Colony Stimulating Factor (G-CSF), an interleukin, immunoglobulin, and fragments thereof.

9. The polypeptide of claim 4, wherein said second polypeptide is selected from the group consisting of erythropoietin (EPO), thrombopoietin (TPO), granulocyte-macrophage Colony Stimulating Factor (GM-CSF), granulocyte Colony Stimulating Factor (G-CSF), an interleukin, immunoglobulin, and fragments thereof.

10. The polypeptide of claim 5, wherein said second polypeptide is selected from the group consisting of erythropoietin (EPO), thrombopoietin (TPO), granulocyte-macrophage Colony Stimulating Factor (GM-CSF), granulocyte Colony Stimulating Factor (G-CSF), an interleukin, immunoglobulin, and fragments thereof.

11. The polypeptide of claim 1, wherein said polypeptide comprises a mutation at the dimerization interface of a flt3-L dimer.

12. The polypeptide of claim 11, wherein said mutation is at position 26, 27 or 64 of the mature wild type flt3-L polypeptide (SEQ ID NO:18).

13. The polypeptide of claim 11, wherein said polypeptide comprises a mutation selected from the group consisting of L26F (SEQ ID NO:12), L27P (SEQ ID NO:13) or A64T (SEQ ID NO:9).

14. The polypeptide of claim 2, further comprising a mutation at the dimerization interface of a flt3-L polypeptide.

15. The polypeptide of claim 1, wherein said polypeptide has an altered charge distribution from that of the wild type human flt3-L full length polypeptide (SEQ ID NO:1) or mature human flt3-L polypeptide (SEQ ID NO:18).

16. The polypeptide of claim 15, wherein at least one amino acid of the wild type flt3-L polypeptide has been substituted by a basic residue.

17. The polypeptide of claim 16, wherein said substitution occurs in the region corresponding to positions 118-124 of the mature wild type flt3-L polypeptide (SEQ ID NO:18).

18. The polypeptide of claim 17, wherein said substitution is at position 118 or position 122 of the mature wild type flt3-L polypeptide (SEQ ID NO:18).

19. The polypeptide of claim 15, wherein at least one basic residue has been added to the full length wild type flt3-L polypeptide (SEQ ID NO:1) or the mature wild type human flt3-L polypeptide (SEQ ID NO:18).

20. The polypeptide of claim 15, wherein a basic amino acid of wild type flt3-L has been replaced with another amino acid.

21. The polypeptide of claim 19, wherein said basic amino acid is the Lys at position 84 of mature human wild type flt3-L (SEQ ID NO:18).

22. The polypeptide of claim 1, wherein said mutant flt3-L polypeptide comprises amino acids 28-160, 28-182 or 28-185 of the full length human wild type flt3-L polypeptide (SEQ ID NO:1).

23. An isolated nucleic acid encoding a polypeptide of claim 1.

24. An isolated nucleic acid encoding a polypeptide of claim 2.

25. An isolated nucleic acid encoding a polypeptide of claim 3.

26. An isolated nucleic acid encoding a polypeptide of claim 4.

27. An isolated nucleic acid encoding a polypeptide of claim 5.

28. An isolated nucleic acid encoding a polypeptide of claim 6.

29. An isolated nucleic acid encoding a polypeptide of claim 7.

30. An isolated nucleic acid encoding a polypeptide of claim 8.

31. An isolated nucleic acid encoding a polypeptide of claim 9.

32. An isolated nucleic acid encoding a polypeptide of claim 10.
33. A method of inducing cellular expansion, comprising the steps of:
isolating a population of cells to be expanded; and
exposing said cells to a mutant flt3-L polypeptide, to produce an expanded cell population.
34. The method of claim 33, wherein the expanded cell population is introduced into a patient.
35. The method of claim 33, wherein the population of cells to be expanded comprises hematopoietic cells.
36. The method of claim 33, wherein the population of cells is also exposed to a growth factor in addition to said flt3-L mutant polypeptide.
37. The method of claim 33, wherein said growth factor is selected from the group consisting of interleukins, colony stimulating factors, and protein kinases.

38. A method of expanding a population of cells *in vivo*, comprising the step of administering to a subject a pharmaceutical composition of mutant flt3-L polypeptide or nucleic acid encoding such polypeptide sufficient to induce the expansion of a target cell population.

39. The method of claim 38, wherein the target cell population is isolated from the group consisting of hematopoietic cells, NK cells or dendritic cells.

40. The method of claim 38, wherein the pharmaceutical composition further comprises a growth factor in addition to said flt3-L mutant polypeptides.

41. The method of claim 40, wherein said growth factor is selected from the group consisting of interleukins, colony stimulating factors and protein kinases.

42. A method of modulating an immune response in a subject, said method comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition comprising a flt3-L mutant polypeptide or nucleic acid encoding such polypeptide.

43. A method of treating an immune disorder in a subject, said method comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition comprising a flt3-L mutant polypeptide or nucleic acid encoding such polypeptide.

44. The method of claim 43, wherein said disorder is selected from the group consisting of allergy, immunosuppression, and autoimmunity.

45. A method of treating a pathological condition, said method comprising the step of administration of a pharmaceutical composition of flt3-L mutant polypeptide or nucleic acid, wherein said condition is selected from the group consisting of myelodysplasia, aplastic anemia, Human Immunodeficiency Virus infection, breast cancer, lymphoma, small cell lung cancer, multiple myeloma, neuroblastoma, acute leukemia, testicular cancer and ovarian cancer.

46. A method of inducing cellular differentiation, said method comprising the steps of:

isolating a target population of cells; and

administering an amount of flt3-L mutant polypeptide sufficient to induce the production of differentiated cells.

47. The method of claim 46, wherein said target population of cells comprises hematopoietic cells.

48. The method of claim 47, wherein the differentiated cells are selected from the group consisting of Natural Killer (NK) cells, facilitating cells, or dendritic cells.

49. A method of treating a patient, comprising administering to said patient the differentiated cells produced by the method of claim 46.

50. The method of claim 49, further comprising the step of administering a growth factor to the patient.

51. The method of claim 49, wherein said growth factor is selected from the group consisting of interleukins, colony stimulating factors and protein kinases.

52. A method of augmenting an immune response in a patient, comprising the step of administering an amount of a flt3-L mutant polypeptide to the patient sufficient to generate an increase in the number of the patient's dendritic cells.

53. The method of claim 52, wherein the patient has an infectious disease.

54. The method of claim 53, wherein the infectious disease is HIV.

55. The method of claim 52, wherein the patient has a cancerous or neoplastic disease.

56. A method of enhancing a mammal's immune response to a vaccine antigen, comprising the steps of administering to said mammal an immunogenic amount of the vaccine antigen and an immunogenicity-augmenting amount of a flt3-L mutant polypeptide in concurrent or sequential combination with said vaccine antigen.

57. A method for identifying residues involved in receptor binding in a receptor-ligand system, said method comprising the steps of:

subjecting a nucleic acid population encoding said ligand to mutagenesis, to form a mutagenized ligand population;

transforming cells with said mutagenized ligand population, to form transformed colonies;

transferring said transformed colonies to a first membrane;

overlaying said first membrane with a second membrane, said second membrane being coated with capture means for capturing said ligand and mutants thereof;

reacting said second membrane with a receptor for said ligand; and

subsequently reacting said second membrane with means for detecting receptor binding to said ligand or mutants thereof.

58. The method of claim 57, wherein said cells are selected from the group consisting of yeast cells and bacterial cells.

59. A method of screening to identify mutant polypeptides with altered expression characteristics, said method comprising the steps of:

subjecting a nucleic acid population encoding said ligand to mutagenesis, to form a mutagenized ligand population;

transforming cells with said mutagenized ligand population, to form transformed colonies;

transferring said transformed colonies to a first membrane;

overlaying said first membrane with a second membrane, said second membrane being coated with capture means for capturing said ligand and mutants thereof;

reacting said second membrane with a receptor for said ligand; and

subsequently reacting said second membrane with means for detecting receptor binding to said ligand or mutants thereof.

60. The method of claim 59, wherein said cells are selected from the group consisting of yeast cells and bacteria cells.

61. A mutant Stem Cell Factor (SCF) or Macrophage Colony Stimulating Factor (M-CSF) polypeptide, wherein said polypeptide has an amino acid substitution at a position of said polypeptide corresponding to any one of the regions defined by the amino acid positions 8-15, 81-97 or 116-124 of the mature human wild type flt3-L polypeptide (SEQ ID NO:18) and exhibits increased binding to a flt3 polypeptide compared to wild type SCF or M-CSF.

62. The polypeptide of claim 61, wherein said polypeptide has an amino acid substitution at the position corresponding to position 8, 84, 118 or 122 of the mature human wild type flt3-L polypeptide (SEQ ID NO:18).

63. The polypeptide of claim 61, wherein said polypeptide has an amino acid substitution at the position corresponding to position 8 of the mature human wild type flt3-L polypeptide (SEQ ID NO:18).

64. The polypeptide of claim 63, wherein said mutant polypeptide is a SCF mutant polypeptide.

65. The polypeptide of claim 64, wherein said polypeptide does not bind c-kit.

66. The polypeptide of claim 64, wherein said polypeptide does not bind to mast cells.

67. The mutant polypeptide of claim 61, wherein said mutant polypeptide is M-CSF and has an amino acid substitution at position 9 of the wild type M-CSF polypeptide.

68. A small molecule comprising any one of the regions defined by the amino acid positions 8-15, 81-87 or 116-124 of the mature human wild type flt3-L polypeptide (SEQ ID NO:18), or functional groups corresponding to the side chains of the amino acids within said regions.